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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,460	07/18/2001	Lynn B. Lunsford	08191-014002	1198

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 08/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/909,460	LUNSFORD ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36 and 51-80* is/are pending in the application.

4a) Of the above claim(s) *17,22,24,25,27-32 and 52-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18-21,23,26,33-36 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1, 8, 24, 25, 27, 29, 34, 35, and 51 have been amended, claims 52-80 have been added by the amendment filed on July 30, 2003.

Applicant's response dated January 14, 2004 has been considered, and is found partially persuasive. The response is found partially persuasive because the limitation reciting "which microparticle does not comprise a liposome and a cell" when added to the presently pending claims, is in fact an embodiment which was originally embraced by the generic claim. As such, all previously examined claims, wherein all of which are limited to a combination of microparticles of less then 20 microns in diameter, which have been amended to include limitation reciting "which microparticle does not comprise a liposome and a cell", would continue to be examined. However, newly added claims 52-80 will not be examined because all of the newly added claims are not directed to either (a) a combination microparticles of less than 20 microns and which are not encapsulated in a liposome and does not comprise a cell, or (b) a combination microparticles of less than 20 microns and a nucleic acid sequence encoding an expression product with the provisions as set forth in the Markush group as set forth in the base claim 8.

Claims 52-80 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Claims readable on non-elected species, *e.g.,* claims 17, 22, 24, 25, 27-32 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species.

Elected claims 1-16, 18-21, 23, 26, 33-36, 51 are pending for examination.

The newly added the limitation reciting "which microparticle does not comprise a liposome and a cell", was not recited anywhere in the originally filed claims, and thus, was not searched originally by the examiner prior to issuing the previously mailed first office action. As such, the limitation necessitates the following new ground of rejection.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. ' 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. ' 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Mathiowitz (US Pat No. 6,677,313) *or* Jones *et al.* (Int'l Meeting on Nucleic Acid Vaccines, 1996), taken with Rolland (US Pat No. 6,040,295) and Lee (US Pat No. 5,908,777).

Mathiowitz teach a gene delivery method of employing a plurality of microparticles comprising a polymeric microparticles that are sized between one and ten microns, a stabilizer such as anhydride monomers, oligomers, organic dyes or metal compounds, and a plasmid DNA coding for a protein of interest such as an antigenic polypeptide, wherein the microparticles are delivered to a mucosal tissue such as vagina tissue, *e.g.,* see column 2, lines 17-56, column 4, last par., columns 7 and 8, and columns 12 and 13. Plasmid vectors including a targeting ligand is disclosed on column 19, lines 21-23.

Jones teaches a method of employing microparticles having a diameter of no more than 10 ug composed o PLGA for delivering supercoiled plasmid DNA coding for any immunogenic protein known in the prior art (entire document). Route of administration including delivery into a mucosal tissue is also taught in Jones. Jones also teaches ratio by weight that encompasses the ratios employed in the as-filed specification.

Neither Mathiowitz nor Jones teaches an incorporation of a lipid based compound(s) into the microparticles, wherein the lipid based compound(s) are complexed and/or stabilizes the plasmid DNA(s) contained therein.

However, at the time the invention was made, Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations, *e.g.,* those formulated with a carrier or stabilizer such as a cationic polymer (abstract, entire disclosure, particularly column 1 bridging column 2, column 2, second par.. , column 3, last par bridging column 4). An addition of a targeting ligand to the microparticles and/or plasmid is also taught by Rolland so as to enhance the expression of the complexed plasmid vectors at a desired target tissue (column 2, line 45). An incorporation of stabilizer(s) and/or trafficking peptide so as to enhance transcription, translation, transcript stability, replication, and intracellular trafficking are disclosed on columns 2 and 3 as being conventional in the prior art. More importantly, Rolland teaches on columns 3 and 4 that compounds which are known to help to prolong the bioavailability of a nucleic acid, *e.g.,* protecting the nucleic acid, concentrating a nucleic acid, indirectly facilitating uptake of a nucleic acid, such as polymers, oils (a lipid based compound), surfactants can be suitably used to enhance the bioavailability of a nucleic acid. Phosphatidylcholines (lecithins) are listed on column 4, line 53 as one of the compounds, which exhibits amphipathic properties that are deemed essential for the intended function of prolonging the bioavailability of a nucleic acid. A specific example of an oily suspension which comprises a PVP based polymer/DNA polymer blended in sesame oil with 0.1% Tween-80 is disclosed on column 4, last par.

In addition, Lee teaches that a lipidic carrier based composition composed of a polycation, an anionic lipid, and a stabilizer such as CTAB (employed as a second lipid), functions as to reduce plasmid degradation due to its immunogenicity and to enhance transfection activity (abstract, column 3, lines 39-59, and column 6, lines 23-52). On column 7, first paragraph, Lee teaches that any known lipidic material can be substituted to form lipidic vectors such as anionic oil-in-water emulsions or micelles.

As such, it would have been obvious for one of ordinary skill in art to employ known lipid based stabilizer/enhance such as those disclosed in Rolland and/or a known lipid based carrier such as those anionic lipid based complex of Lee as a stabilizer and/or are formulated agent of the plasmid vector contained in the microparticles of Mathiowitz or Jones. One of ordinary skill in the art would have been motivated to employ any known lipid based stabilizer and/or agents formulated specifically for plasmid vectors including those disclosed in Rolland and/or Lee, respectively, in order to prepare a condensed plasmid vector for use in the microparticles of Mathiowitz or Jones because Rolland teaches that not only polymeric microparticles containing lipid based stabilizers can be used to enhance and prolong the bioavailability of plasmid vectors encoding a product of interest, the microparticle composition can also be used to do the same with nucleic acid plasmid vectors formulated with a carrier such as cationic lipid. One then would also have been motivated to employ the lipidic vector based formulation of Lee as a complex with the plasmid vector of Mathiowitz because such lipidic based formulation would function as to reduce plasmid degradation

due to its immunogenicity and to enhance transfection activity. One would also have expected from the combined cited references that such enhancements including those driven by a lipid based carrier when complexed with a plasmid vector expressing an antigen would help to increase to stabilize the plasmid vector when circulated *in vivo* or released from the microparticles, thereby enhancing recognition by an immune response to the expressed antigens at a target site such as a mucosal tissue.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 8-16, 18-22, 26, 34-36, and 51 are rejected under 35 USC 103(a) as being unpatentable over either Mathiowitz (US Pat No. 6,677,313) *or* Jones *et al.* (Int'l Meeting on Nucleic Acid Vaccines, 1996), taken with Rolland and Lee (US Pat No. 5,908,777), and further in view of either Carson (US 2003/0109469) taken with Adema (US Pat No. 6,500,919).

As set forth in the immediately preceding paragraphs, the combined Mathiowitz or Jones, taken with Roland and Lee references teach, suggest and provide a motivation to employ microparticles which are less then about 20 um in diameter, formulated lipid agent(s) and plasmid DNA contained therein for use in delivering and expressing an immunogenic polypeptide in a desired subject. The combined cited references do not teach explicitly that the immunogenic polypeptide includes a peptide that binds to a MHC class I molecule, that an array of antigenic peptides can be constructed in the plasmid vectors, and that a trafficking sequence can also be linked to the expressed peptide.

However, at the time the invention was made, the concept of employing a peptide or arrays of peptides known in the prior art in a plasmid expression vector for use as an immunogenic composition is taught in Carson. For example, par. 59-60 on page 10-11 discloses that the plasmid vector can be constructed to encode an array of antigenic peptides of choice such as MHC peptides, cytokines, and/or T cell epitopes for tumor treatment, for example. As evidenced by Adema, MHC I binding peptides for use in vaccines such as treatment of a melanoma tumor are well-known in the prior art.

In addition, Urban teaches that it is also advantageous and/or routine to link a trafficking signal to antigenic peptides so as to target proteins/peptides to specific intracellular compartments (column 13, second par.).

Thus, it would have been obvious for one of ordinary skill in the art to employ an antigenic peptide of choice such as any known MHC I binding peptide or a combination thereof in the plasmid vector taught by the combined Mathiowitz or Jones, Rolland, and Lee references. One of ordinary skill in the art would have been motivated to employ one more DNA fragments coding for peptides in the plasmid expression vector because Carson teaches on page 11 that the use of plasmid vector expressing an array of peptides of choice can be routinely made and is efficient to be used as a cocktail vaccine against more than antigens of choice, and because Adema teaches that MHC I binding peptides are effective for use in vaccine against tumor bearing patients such as melanoma patients.

It would also have been obvious for one of ordinary skill in the art to have employed or incorporated stabilizer compounds, two or more expression cassettes encoding two distinct and/or overlapped MHC-I binding peptides, antigenic protein sequences and/or immune response regulators, specifically second lipid compounds including CTAB, phospholipid and phosphatidylcholine, or an endoplasmic reticulum (ER) directed peptide in the preparations of microparticles described in the combined cited references for use in a DNA transfection method. One of ordinary skill in the art would have been motivated to have employed known enhancers and/or stabilize compounds and/or targeting peptide sequences and/or a trafficking peptide linked to an antigenic peptide of choice in the microparticles or plasmids contained therein because such modifications are routinely employed in the art of making lipids and/or polymers for use as a carrier for enhancing the delivery of a DNA into the cytosol of a target cell, as evidenced by the disclosures and references cited by applicants and the specific prior art employed in this stated rejection. The use of a trafficking signal as an additional element for linking to an immunogenic peptide would also have been obvious to one of ordinary skill in the art because Urban teaches that the signal can be advantageously used to traffic an immunogenic peptide as desired.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 1-16, 18-21, 23, 26, 33-36, 51 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable

over claims 1-32 of US patent No. 5,783,567 taken with Rolland and Lee, and application's admission over the prior art on page 40 of the as-filed specification.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are readable on a polymeric composition comprising a polymer microparticle, and DNA, wherein the polymeric microparticle is less than about 20 microns, and method of using the polymeric composition to deliver an encoded DNA molecule to a subject.

To the extent that the claims of the patent does not claim the use of a lipid compound including anionic lipid compound in the microparticle preparation, it would have been obvious to one of ordinary skill in the art that claims readable on lipid contained microparticles are obvious variants of the claims cited in the patent because both Rolland and Lee, and applicant's admission over the prior art all teach advantages of employing a lipid based compound as adjuvant or DNA carriers, respectively. One of ordinary skill in the art would have been motivated to employ any known lipid based stabilizer and/or agents formulated specifically for plasmid vectors including those disclosed in Rolland and/or Lee, respectively, in order to prepare a condensed plasmid vector for use in the microparticles of Mathiowitz or Jones because Rolland teaches that not only polymeric microparticles containing lipid based stabilizers can be used to enhance and prolong the bioavailability of plasmid vectors encoding a product of interest, the microparticle composition can also be used to do the same with nucleic acid plasmid vectors formulated with a carrier such as cationic lipid. One would also have expected that a lipid based vector such as those disclosed in

Lee, when incorporated into the microparticles, would act as an effective carrier and/or stabilizer of plasmid vectors contained therein, *e.g.,* helping an increase of an immune response directed toward a desired antigen, that a lipid when complexed to a plasmid vector, would cause stabilization of the plasmid DNA and its subsequent expression at a desired site, and that negative charged lipids are routinely employed in the prior art as carrier for biologically active molecules.

Applicant's latest response is moot in view of the new grounds of rejection.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0804.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER